FOOD INTAKE AND THE REGULATION OF BODY WEIGHT

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Abstract: This chapter reviews the recent literature on hormonal and neural signals critical to the regulation of individual meals and body fat. Rather than eating in response to acute energy deficits, animals eat when environmental conditions (social and learned factors, food availability, opportunity, etc.) are optimal. Hence, eating patterns are idiosyncratic. Energy homeostasis, the long-term matching of food intake to energy expenditure, is accomplished via controls over the size of meals. Individuals who have not eaten sufficient food to maintain their normal weight have lower levels of adiposity signals (leptin and insulin) in the blood and brain, and one consequence is that meal-generated signals (such as CCK) are less efficacious at reducing meal size. The converse is true if individuals are above their normal weight, when they tend to eat smaller meals. The final section reviews how these signals are received and integrated by the CNS, as well as the neural circuits and transmitters involved.

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INTRODUCTION

Tremendous advances are being made in our understanding of the physiology of food intake. There are many reasons for this, perhaps foremost being the revolution in molecular biology and its application to behavior. A different, albeit not totally independent, factor has been a change in the federal government’s view of obesity and its treatment (see World Health Org. 1998). Obesity is now recognized as a chronic disorder with biologic causes that may require chronic medical therapy, much as is the case for hypertension or diabetes mellitus. Prior to this change of policy, antiobesity drugs approved by the Federal Drug Administration were expected to induce weight loss that was sustained even after drug treatment was discontinued. Consequently, there was little interest on the part of pharmaceutical companies in the development of new drugs for the treatment of obesity. Fortunately, common sense and the weight of medical evidence prevailed and led to a reassessment. A major consequence of this new policy is the potential for new opportunities for the pharmaceutical industry, which once again has turned its attention (and immense resources) toward the development of antiobesity drugs and their lucrative market.

A second major contributor to the accelerating pace of research on the controls of food intake was the discovery in 1994 of the adipose tissue hormone leptin (Zhang et al 1994) and the finding that it interacts with specific receptors in the brain to control food intake and energy homeostasis. The realization that specific gene products have a profound influence on food intake and body weight paved the way for biotechnology companies to enter the fray, and the stream of new gene products and drugs that are now under investigation is impressive. One consequence is that the center of gravity of research on food intake has spread from its roots in psychology and physiology toward biochemistry and molecular biology, and many investigators new to the field are making seminal observations. In this review we attempt to unravel some of the myriad new molecules important in the control of eating and integrate them into what is understood about the biology of energy homeostasis.

ENERGY HOMEOSTASIS

Food intake serves many purposes. It provides energy in the form of calories as well as all the macronutrients, with their essential building blocks for cellular structure and function, vitamins, and minerals, and a variable amount of water. We focus on the intake of calories and its regulation while recognizing that regulation of specific macro- and micronutrients also occurs, often in the form of specific appetites, and that these can interact with the intake of calories. Energy intake in the form of food, and energy expenditure in the form of cellular metabolism and exercise, are precisely coupled over long intervals in healthy adults,
resulting in stable body fat stores. The processes that regulate these behaviors are collectively called energy homeostasis.

PATTERNS OF FOOD INTAKE

Humans enjoy diverse lifestyles, and this complexity is reflected in their eating customs and habits. Although the stereotyped “three meals a day” may typify many individuals, both the number and size of eating bouts, as well as the total amount of food consumed each day, tend to be variable (de Castro 1998). There is also considerable day-to-day variability within individuals as they integrate eating with other activities. Yet, assuming that adequate food is available in the environment, most individuals (at least as adults) maintain relatively stable amounts of stored fat (adiposity) over long intervals (Bray 1976, Schwartz & Seeley 1997b, Stallone & Stunkard 1991). This implies that energy intake and expenditure are matched to one another despite a considerable variety of eating patterns.

Energy is continuously expended by living organisms, the rate varying with activity, ambient temperature, and many other factors. By comparison, eating generally occurs in distinct bouts or meals, the size and number of which vary considerably both within and among individuals. Vertebrates are able to cope with this variability because they store excess caloric energy when ample food is available and draw on those reserves when times are leaner. This natural ebb and flow of energy is easily illustrated by seasonal fluctuations of energy balance in many species, with more food being available, consumed, and stored as energy in the summer and autumn and with fat reserves becoming depleted again in the winter. But analogous fluctuation occurs on a daily basis as well, with the organism living off recently ingested energy during and immediately after meals and storing the excess to support bodily activities until it eats again. The entry of calories into the blood from either the gut or energy stores, as well as the uptake and utilization of these calories by the various tissues, is controlled by the brain and the liver. Both organs detect energy available in the blood, and the two intercommunicate via direct neural connections. The liver additionally has the ability to convert energy from one molecular form to another (e.g. from carbohydrate to fat, or from amino acids to carbohydrate) as needed, and it is the primary site for delivery of glucose to the circulation when glucose is no longer being absorbed from the gastrointestinal tract. This is important because some tissues rely relatively exclusively on one or another molecular form of energy (the brain has a large obligatory glucose requirement and the liver must utilize fats), whereas others (e.g. skeletal muscle) utilize whatever is available (glucose or fats).

Concordant with its continuous need for adequate levels of energy derived from fat, the liver is able to detect local reductions of fat availability and/or usage. In response, the liver activates distinct neural pathways that enter the brainstem

**MEAL INITIATION**

The brain and liver are incredibly efficient at controlling the provision of what is needed, and as a result, adequate amounts of utilizable fuels (glucose and fats) are generally always available to tissues via the blood. Fluctuations in the circulating levels of these fuels generally occur only during and after meals as ingested energy passes from the gut into the circulation, and from there into tissues and energy storage organs. Decreases of plasma fuels below levels adequate to meet tissue requirements are rare in normal individuals although they can be experimentally induced. For example, if the amount of energy derived from glucose is decreased, either by drugs that deplete it from the blood [exogenous insulin (Grossman 1986, Lotter & Woods 1977, MacKay et al 1940)] or drugs that prevent its cellular oxidation [2-deoxy-D-glucose (Grossman 1986, Smith & Epstein 1969)], an emergency situation occurs as the brain detects its requisite fuel supply dwindling. One result is that animals seek and ingest food (Langhans 1996a). Likewise, if fat consumption is experimentally compromised (Langhans & Scharrer 1987b, Scharrer & Langhans 1986), the source of usable fuel by the liver is challenged, the liver sends critical neural messages to the brain, and again animals seek and ingest food (Langhans 1996a,b).

A key point is that under usual circumstances, the supply of energy in the blood does not decrease to anywhere near the threshold necessary to trigger eating. Rather, animals initiate meals even though ample energy is readily available. Eating is in fact a relatively inefficient way to get calories into the blood rapidly. Unless pure glucose is available (rare in natural settings), foods must be processed and digested in the stomach, passed to the intestine where they are further processed, and then absorbed into the blood. Despite this time lag between the ingestion of food and the appearance of nutrients in the bloodstream, the concept that
eating is triggered as a means to replenish dwindling fuel supplies has persisted for many decades. Early in this century blood glucose was thought to be a critical determinant of meals (Carlson 1916), and this concept was formalized and popularized by Mayer with his glucostatic hypothesis (Mayer 1955, Mayer & Thomas 1967). In a nutshell, Mayer postulated that eating is initiated when glucose availability and utilization by specific cells in the hypothalamus are reduced. Analogously, meals were hypothesized to terminate when glucose levels and/or availability are restored to adequate levels. Besides the problem of the temporal sluggishness, such a process forces animals to attain dangerously low levels of glucose prior to the initiation of every meal. More important, it is not clear what the consequences would be if glucose availability dipped to the threshold for initiating meals at a time when it was inconvenient or impossible to eat. It is now generally recognized that this protective system is probably activated to the point of initiating a meal only in extreme metabolic emergencies (Epstein et al 1975, Grossman 1986, Langhans 1996a).

**Correlates of Meal Onset**

Nonetheless, when the level of glucose in the blood is continuously monitored by means of an indwelling intravenous catheter, Campfield & Smith (1986b, 1990b) observed that beginning a few minutes prior to when a “spontaneous” meal is initiated in freely feeding rats, blood glucose decreases. More recently, that group reported a similar phenomenon in humans (Campfield et al 1996). This is an important observation because, at least in rats, every observed spontaneous meal was preceded by the small (approximately 12%) but reliable decline of plasma glucose (Campfield et al 1985). The premeal decline of blood glucose reverses just prior to the actual initiation of eating, and if food is removed at that point (and no eating occurs), glucose returns to the baseline that was present before the decline began. Campfield & Smith interpreted the premeal glucose decline as providing a signal that is monitored by the brain (Campfield & Smith 1990a,b; Smith & Campfield 1993). When its parameters are “correct,” a meal is initiated. If metabolic conditions preclude the decline meeting the “correct” parametric criteria, no meal is initiated. In their schema, Campfield & Smith believe that the brain is the initiator of the decline of plasma glucose. Consistent with this, there is a small increase of plasma insulin at the beginning of the premeal decline of glucose (Campfield & Smith 1986a, 1990a), and cutting the vagus nerve (via which the brain can regulate insulin secretion) disrupts the relationship between changes of glucose and the start of meals (Campfield & Smith 1990a). One particularly appealing aspect of the hypothesis that premeal declines of glucose trigger meals is that extreme life- or consciousness-threatening declines of glucose need not be present for normal meals to occur. It also suggests that small, physiological fluctuations of glucose provide important signals that the brain uses to help determine ingestive responses. There is also evidence that the liver responds to small fluctuations of fatty acids and their metabolites by sending
signals to the brain via the vagus nerves (Langhans et al 1985, Langhans & Scharrer 1987a).

There are other events that occur prior to, and hence are predictive of, the onset of meals. Implanted thermistors allow body temperature to be monitored continuously in freely moving and feeding animals. Just prior to spontaneous meals, the body temperature of rats begins to increase (de Vries et al 1993). When the meal begins, temperature continues to increase and then declines as the meal is terminated. Likewise, metabolic rate has been found to decrease prior to the start of spontaneous meals, and to increase as eating begins (Even & Nicolaides 1985, Nicolaides & Even 1984). All these parameters (blood glucose, temperature, metabolic rate, and no doubt others as well) begin a slow change 10–15 min before meals begin, and all are therefore highly correlated with meal onset. With a slightly different time course, laboratory rats increase their activity (e.g. running in a wheel) prior to spontaneous meals (Aravich et al 1995, Rieg & Aravich 1994, Sclafani & Rendel 1978, Stevenson & Rixon 1957). All these observations support the hypothesis that animals eat because these changes are occurring, i.e. that the decrease of blood glucose or of metabolic rate, or the exercise-induced use of fuels, is causally related to meal onset. However, a compelling case can also be made that, based upon factors such as habit or opportunity, the brain determines when a meal is going to start, and that as part of the overall meal process it initiates metabolic changes to prepare the body to receive the food (Woods & Strubbe 1994). As an example, a premeal decline of blood glucose can limit the magnitude of the otherwise much larger postprandial increase of blood glucose. In this schema, animals do not initiate meals because one or another tissue’s supply of available energy is about to be compromised, but rather an animal eats when it is accustomed to eating, or when its predators have left, or when it has a break between classes. We take the position that the timing of meals is idiosyncratic and dictated by an individual’s lifestyle, convenience, and opportunity. This accounts for the extreme variability of meal patterns among individuals in a species, but it cannot account, by itself, for the remarkable ability of animals to maintain a constant level of adiposity.

The Role of Learning

An important question concerns the factors that actually cause an individual to initiate a meal, or to experience “hunger.” That is, if, under normal conditions, decreases of blood glucose or fats (or their correlated utilization) do not cause an animal to eat, what does? Although there are no clear answers to this question, there are compelling data that environmental stimuli previously associated with the ingestion of calories can elicit eating (Sclafani 1997, Warwick 1996, Woods & Strubbe 1994). Time of day is a particularly salient cue (Woods & Strubbe 1994), and a large literature documents the observation that when animals are habitually fed at the same, arbitrarily-selected time each day, they learn to synthesize and secrete hormones and neurotransmitters that are important controllers
of food intake [e.g. insulin (Woods et al 1996, 1977) and neuropeptide Y (Yoshii-hara et al 1996a,b)]. Animals readily learn associations based upon the caloric content of food they receive, and the later presence of these cues in turn contributes to how much food is consumed during meals (Sclafani 1997, Warwick & Schiffman 1992). There is even evidence that the ability of “satiety” factors such as cholecystokinin (see below) to reduce meal size is modifiable by learning (Goodison & Siegel 1995). Finally, the argument has been made that diurnal fluctuations of hormones and neurotransmitters that are important determinants of meals and meal size are in fact entrained to the time that animals normally eat the largest meals of the day (Woods & Strubbe 1994). It is therefore reasonable to conclude that based upon an individual’s history, idiosyncratic stimuli in the environment contribute to the timing of meals, and that associations based upon the caloric (and nutrient) content of previously consumed foods contribute to how much is eaten (e.g. Altizer & Davidson 1999, Davidson et al 1997, Sclafani 1997, Warwick & Weingarten 1996).

THE CONTROL OF MEAL SIZE

Given that the timing and frequency of meals are driven more by lifestyle than by immediate need, and given that caloric intake is matched to caloric expenditure over long intervals, the regulation of energy homeostasis can be manifest via control of how many calories are consumed when eating actually occurs. In other words, energy homeostasis can be achieved if there is control over meal size. Consistent with this, there is compelling evidence that the amount of food consumed during individual meals is under the control of signals generated in response to the food being eaten (Smith 1998, Smith & Gibbs 1992). And there is further evidence that the sensitivity of the brain to these meal-generated signals is in turn determined in part by the size of the adipose mass. That is, when animals are administered compounds that indicate to the brain that body fat has increased (leptin or insulin, see below), they become far more sensitive to the meal-suppressing action of meal-generated signals such as cholecystokinin (CCK) (Barrachina et al 1997, Figlewicz et al 1995, Matson & Ritter 1999, Matson et al 1997, Riedy et al 1995). The point is that an individual who has recently eaten insufficient food to maintain its weight will be less sensitive to meal-ending signals and, given the opportunity, will consume larger meals on the average. Analogously, an individual who has enjoyed excess food and consequently gained some weight will, over time, become more sensitive to meal-terminating signals.

Gibbs et al (1973) were the first to demonstrate conclusively that certain meal-generated peptides are able to reduce meal size, and more recently Smith & Gibbs (1992) provided a theoretical framework to account for these observations. It is based upon the well-described process that occurs when ingested food interacts with receptors in the proximal intestine. General omnivores such as humans and rats consume a wide spectrum of foods. Consistent with this, their digestive sys-
tems can draw on an analogously wide spectrum of digestive enzymes and secretions to customize the digestive process with what has actually entered the gut. This is accomplished via sensors in the mouth and digestive tract that analyze what is consumed and that coordinate the precise blend of digestive juices to be added to the food and that control the speed with which the material moves through the system. Enteroendocrine sensory cells lining the gut secrete compounds that signal distant organs such as the liver and exocrine pancreas to release the appropriate secretions into the intestine. Smith & Gibbs (1992) postulated that some of these secreted compounds (mainly peptides) additionally stimulate sensory nerves and thereby provide a signal related to the number and type of calories being consumed to the brain. The brain consequently integrates this information with other controllers and thereby determines meal size.

The gut peptide CCK is the best-known example of these meal-generated and meal size-controlling signals. CCK is secreted by the intestines during normal meals, and there are specific receptors for it, among many other places, on sensory fibers of the vagus nerve near the point where food passes from the stomach into the intestine (Smith et al. 1984). More precisely, these vagal nerve endings contain CCK-A receptors (Corp et al. 1993, Mercer & Lawrence 1992). Hence, during a meal, locally secreted CCK can stimulate these nerves and thereby send a signal to the lower brainstem where they synapse with neurons controlling digestive reflexes and responses as well as with neurons passing anteriorly to the forebrain (see Moran & Schwartz 1994, Rinaman et al 1995). When selective CCK-A receptor antagonists are administered to animals prior to a meal (Hewson et al. 1988, Moran et al 1993, Reidelberger & O’Rourke 1989), meal size is increased significantly. Such results imply that endogenous CCK normally acts to reduce meal size. Consistent with this, if exogenous CCK is administered prior to a meal, meal size is decreased significantly and dose dependently (Gibbs et al 1973; Kulkosky et al 1976; Smith & Gibbs 1992, 1998). The importance of the CCK-to-vagus-to-brainstem circuitry is revealed when the receptive fields of the sensory fibers (Moran et al 1988), the sensory fibers themselves (Smith et al 1981, Smith et al 1985), or their entry point into the brainstem (Edwards et al 1986) is compromised. In each instance, exogenous CCK no longer reduces meal size. Consistent with these observations, when these same sensory fibers have been acutely compromised, there is an increase of meal size, which suggests that they normally send signals to the brain that limit intake (Chavez et al 1997, Kelly et al 1999).

Several further points can be emphasized. One is that the reduction of meal size elicited by exogenous CCK occurs at doses that do not create malaise (for reviews, see Smith & Gibbs 1992, 1998). Another is that the sensations elicited by CCK comprise but one portion of meal-related signals that influence meal size. There are several other gut peptides that have similar actions, although the route(s) by which their signals are passed to the brain differs. These include members of the bombesin family of peptides (gastrin releasing peptide and neuromedin B in mammals) (Gibbs et al 1979, Smith & Gibbs 1998), glucagon (Geary 1998, Salter...
There are also other kinds of signals that normally help limit meal size, including the amount of distension or stretch in the stomach. Endings on vagal sensory nerves in the muscle layers of the stomach are situated to function as tension or stretch receptors. These same nerves have other branches with different kinds of sensory endings (Berthoud & Powley 1992), which suggests that two or more kinds of sensory information can be integrated within single vagal neurons. Consistent with this anatomical observation, it was recently reported that vagal activity elicited by exogenous CCK combines synergistically with that caused by distension of either the stomach (Schwartz et al 1993) or the duodenum (Schwartz et al 1995). The important point is that signals conveying information about numerous key parameters related to food intake converge in the brainstem (Schwartz & Moran 1996, Wang et al 1998). These include, in addition to gastric stretch, information on the specific types and amounts of food being processed, the relative amounts of water and solutes, the possible presence of toxins in the food, and so on.

THE REGULATION OF ADIPOSITY

In most adult mammals, the level of adiposity tends to remain constant over long intervals (Bray 1976, Keese & Hirvonen 1997, Schwartz & Seeley 1997b, Stallone & Stunkard 1991). This is in spite of the fact that daily energy intake and expenditure, as well as meal patterns, may vary considerably over the same intervals. This is usually explained in thermodynamic terms, i.e. the energy equation tends to be balanced over long intervals (Keesey & Hirvonen 1997). Energy that is expended through metabolism, heat production, and physical exercise is precisely matched by energy that is consumed, for even a small discrepancy between the two will lead to gradual weight gain or weight loss. The precision of the regulatory mechanism is revealed when the system is perturbed. If an individual voluntarily diets (or has its food supply forcibly reduced), it loses weight, and the loss is mainly body fat. However, when the diet ends, or the food supply is restored, the individual eats more food than normal and regains the lost weight. Likewise, if individuals voluntarily or experimentally eat sufficient extra food to gain weight, they readily become hypophagic and lose the excess weight when conditions permit. Many reviews have documented these points (Bray 1976, Keese & Hirvonen 1997, Schwartz & Seeley 1997b, Stallone & Stunkard 1991, Woods et al 1974). Even more compelling is the observation that if adipose tissue is surgically removed, the suddenly below-normal-weight individual, if s/he has a nutritionally adequate diet, eats sufficient extra calories to regain the weight lost to the scalpel (Faust et al 1977, 1979). In all these examples, food intake is not the sole means of correcting displaced adiposity. Rather, there are parallel changes
of metabolic rate that work in concert with changes of food intake as adiposity is restored (Keesey & Hirvonen 1997).

There are several important implications of these observations. The first is that the amount of fat in the body is under strict negative feedback control. When it is displaced (whether voluntarily or involuntarily) and free feeding with ample food is allowed, its pre-perturbation level is soon restored. The second is that regulatory control systems in the brain appear to sense the amount of fat that actually exists at any moment. The third is that when perturbations in adiposity occur, the brain has corrective responses at its command that, in this case, control both the amount of calories eaten and the rate that energy is expended.

The size of the adipose mass that individuals maintain and defend obviously varies considerably within a species. Evidence suggests that in humans, the amount of fat carried is a complex interaction of genes and environment (Björntorp 1997b, Bouchard 1995, Comuzzie & Allison 1998, Hill & Peters 1998, Perusse et al 1998, Ravussin & Gautier 1999, Ravussin & Tataranni 1997). It is clear that as environmental conditions change for any given individual, the amount of fat they maintain also changes. For example, persistent exercise (Brownell 1998, Doucet & Tremblay 1998, Rippe & Hess 1998, Saris 1998) or stress (Björntorp 1997a,b) can result in maintenance of altered levels of adiposity. The nutritional content of the diet is also a major factor, with higher proportions of calories consumed as fat being associated with maintaining a greater amount of adiposity (Bray & Popkin 1998, Hill & Peters 1998, Willett 1998). There is also evidence that nutritional factors present during critical periods of development are important (Jackson et al 1996; West et al 1982, 1987). An important principle, however, is that in any given environment, an individual will maintain and defend a specific amount of body fat, and whereas changing the environment may change the absolute level of fat maintained, it does not interfere with the ability to regulate.

The regulation of body weight can be likened to the regulation of other homeostatically controlled variables, such as body temperature. Being homeotherms, mammals are able to maintain relatively constant internal temperatures in the face of variable and often extreme ambient temperatures. This feat is easily accomplished by means of coupled afferent and efferent mechanisms. Thermal receptors in the skin, liver, brain, and presumably elsewhere continuously send messages to the central nervous system (CNS). The CNS in turn combines this information with other relevant information (activity level, needs of various tissues, cognitive information) and adjusts the gain of some subset of possible effector mechanisms (blood flow in superficial veins, breathing rate, perspiration, closing a window, etc). The result is that the temperature inside the body remains relatively constant over time, and it is accomplished via adjustments in both behavioral and autonomic responses (see Gordon 1993, Ramsay & Woods 1997).

Until recently, the mechanisms that transduce body fat into afferent signals to the brain were far-less-well understood. Many traditionally studied sensory systems have specialized receptors that convert mechanical, thermal, or electromag-
Adiposity Signals

At least two circulating compounds meet the criteria for being “adiposity” signals to the brain, the pancreatic hormone insulin and the adipose tissue hormone leptin. Leptin is secreted in direct proportion to the amount of fat stored in individual adipocytes (fat cells), such that leaner individuals secrete less and fatter individuals secrete more leptin (Considine et al 1996, Rosenbaum et al 1996). When an individual fasts (or diets) and loses weight, plasma leptin decreases (Ahren et al 1997, Boden et al 1996, Havel et al 1996, Keim et al 1998); analogously, an increase of energy balance and associated weight gain is associated with an increase in leptin secretion (Ahren et al 1997, Seeley et al 1996). The importance of leptin as an adiposity signal to the brain is revealed by animals that either do not synthesize it [ob/ob mice, which have a mutation in the leptin gene (Zhang et al 1994)] or that have genetic mutations that compromise functioning of the leptin receptor [db/db mice and fatty Zucker, fa/fa rats (Chua et al 1996)]. These animals are characterized by hyperphagia and extreme obesity, and administering small amounts of leptin into the brains of ob/ob mice reverses this syndrome (for reviews, see Schwartz & Seeley 1997a, Seeley & Schwartz 1997, Woods et al 1998).

Insulin is the major hormone that enables tissues to remove glucose from the blood. Hence, its secretion is directly responsive to the level of blood glucose, and its absence (as exists in insulin-deficiency diabetes mellitus) is characterized by elevated blood glucose. Insulin secretion is also directly correlated with adiposity (Bagdade et al 1967, Polonsky et al 1988), and this is true in the resting or basal state as well as in response to elevated blood glucose during and after meals (Bagdade et al 1967, Polonsky et al 1988). The importance of insulin as an adiposity signal to the brain is revealed by the observation that insulin-deficient animals are hyperphagic and that the administration of small amounts of insulin locally into the brain of such animals eliminates their hyperphagia (Sipols et al 1995). Furthermore, the administration of antibodies to insulin into the brain of normal animals increases their food intake (Strubbe & Mein 1977) and body weight (McGowan et al 1992). Insulin-deficient individuals are not obese (like leptin-deficient individuals) in spite of extreme hyperphagia because fat cells cannot store fat in its absence. Hence, the brain of the insulin-deficient individual continuously strives to increase body fat and the excess calories consumed accumulate in the blood and are often lost in the urine.
The important point is that at least two hormones, leptin and insulin, provide important afferent information to the brain. The secretion of each is highly correlated with adiposity, a transport system in brain capillary endothelial cells passes each from the plasma into the brain, specific receptors for each exist in areas of the brain that control energy homeostasis, and manipulation of the levels of either locally within the brain causes predictable changes in food intake and body weight. There are several reviews of this literature (Porte et al 1998, Schwartz et al 1992a, Schwartz & Seeley 1997b, Seeley & Schwartz 1997, Woods et al 1998).

CENTRAL CONTROL MECHANISMS

To modulate energy homeostasis effectively, the actions of leptin and insulin within the brain must be transduced into motor patterns that influence the consumption of food on the one hand and energy expenditure on the other. The anatomical and neurochemical nature of the circuits that are sensitive to leptin and insulin are currently the subject of intense study. Because of this, new information concerning the role of long-described but only recently understood neural pathways is being generated at an unprecedented pace. In particular, neuronal circuits downstream of the initial actions of insulin and leptin are recognized as being attractive targets for pharmaceutical intervention in the treatment of obesity. In this section we provide an overview of this rapidly developing area, emphasizing the actions of leptin within the brain.

Mounting evidence supports the hypothesis that neuronal pathways in the hypothalamus are the primary targets for leptin action in energy homeostasis. Receptors for leptin are found throughout the body, as well as in many areas of the brain. However, the so-called long-form or signaling form of the leptin receptor is expressed in particularly high levels in several cell groups of the medial hypothalamus, including the arcuate (ARC), ventromedial, and dorsomedial nuclei (Baskin et al 1999a,b; Schwartz et al 1996b). It is important that these leptin receptors are located on neurons whose neurotransmitters have been implicated as important mediators of energy homeostasis.

Neuropeptide Y (NPY) is a peptide neurotransmitter that is ubiquitously synthesized in many areas of the brain. However, within the ARC, one group of NPY neurons containing leptin receptors is under the control of local levels of leptin. These neurons in turn project to the paraventricular nuclei (PVN), where NPY is released. Reduced leptin signaling such as would occur when an individual is underweight activates these ARC neurons to synthesize and release more NPY into the PVN (Schwartz et al 1996a, Stephens et al 1995). Increased NPY in the PVN and adjacent regions in turn promotes increased food intake, body weight gain (Kalra et al 1988, Stanley et al 1986), and reduced energy expenditure (Billington et al 1991, 1994). Hence, an individual who is underweight secretes less leptin and consequently activates this NPY-to-PVN pathway, thereby contributing to adaptive behavioral and metabolic responses that promote the recovery of the

This leptin-NPY control system works in both directions. Individuals who are rendered overweight secrete increased leptin (Frederich et al 1995). Increased leptin in turn attenuates the activation of the ARC NPY neurons, simulating the effect that would normally occur in response to elevated body fuel stores (Schwartz et al 1996a,b). Leptin inhibition of orexigenic neuronal pathways in the hypothalamus is therefore proposed as playing a major role in energy homeostasis.

The melanocortins are a family of peptides that include adrenocorticotropin hormone and α-melanocyte–stimulating hormone (α-MSH). Within the hypothalamus, some melanocortins, including α-MSH, have effects on energy homeostasis opposite to those of NPY [i.e. they cause anorexia and weight loss (Tsujii & Bray 1989)]. The precursor of α-MSH, proopiomelanocortin (POMC), is synthesized in a subset of ARC neurons situated just adjacent to those that make NPY (Baskin et al 1999a, Kiss et al 1984). Fasting and its associated weight loss reduce POMC expression in the ARC, and local administration of leptin reverses the reduction, stimulating melanocortin synthesis (Schwartz et al 1997, Thornton et al 1997). Thus, conditions associated with reduced leptin signaling cause increased NPY production and reduced melanocortin production (Schwartz et al 1997, Thornton et al 1997). Moreover, leptin administration to these animals increases hypothalamic POMC while inhibiting NPY gene expression, a combination that may play a major role in leptin’s ability to reduce food intake and body weight. The observation that the long-form of the leptin receptor is expressed by both NPY- and POMC-containing neurons in the ARC suggests that they are direct targets of leptin signaling in the hypothalamus (Baskin et al 1999a, Cheung et al 1997).

Some of the POMC neurons of the ARC project to the PVN where α-MSH (and perhaps other melanocortins) stimulate melanocortin (MC) receptors (specifically, MC3 and MC4 receptors (Schioth et al 1996)). A unique feature of this melanocortin signaling system is the presence of both endogenous agonists (α-MSH) as well as antagonists of MC3 and MC4 receptors. The first endogenous melanocortin agonist to be described was a protein called ‘‘agouti protein’’ that is normally expressed in skin and hair follicles, where it is an endogenous modulator of pigmentation (coat color). ‘‘Agouti’’ mice have a mutation that causes them to express agouti protein in the brain inappropriately. As might be expected, agouti mice have chronically antagonized melanocortin receptors in the brain and are obese (Cone et al 1996, Huszar et al 1997). Furthermore, and consistent with the importance of the leptin-modulated ARC-to-PVN pathway, agouti mice do not reduce their food intake and body weight when administered leptin (Halaas et al 1997). An important implication from these findings is that chronic antagonism at MC3/MC4 receptors produces obesity by reducing the actions of leptin
to initiate a cascade of events that results in increased agonistic activity at MC3MC4 receptors via α-MSH. Consistent with this hypothesis, local administration of antagonists to MC3/MC4 receptors into the brain blocks the actions of exogenous leptin to reduce food intake (Seeley et al 1997). 

Agouti-related protein (AgRP) is a more-recently identified antagonist of MC3/MC4 receptors. Unlike agouti protein, which is normally made only in the skin, AgRP is made in the ARC (Rossi et al 1998, Shutter et al 1997), and its local administration into the brain potently stimulates food intake and weight gain. It is interesting that AgRP is made in the same ARC neurons that make NPY and that they are sensitive to changes in energy balance and leptin signaling (Hahn et al 1998). Thus, conditions associated with weight loss (i.e. reduced leptin signaling to the brain) potently induce both AgRP and NPY expression in these ARC neurons while inhibiting the POMC/α-MSH neurons. As a result, when an individual loses weight, the reduced signal to the brain results in the activation of transmitters that increase food intake and reduce energy expenditure (such as NPY). That results in inhibition of transmitters that reduce food intake and increase energy expenditure (such as α-MSH), and the activation of transmitters that antagonize α-MSH (such as AgRP). As discussed below, this level of complexity and apparent redundancy appear to be characteristic of the central controls involved in energy homeostasis.

The neuronal pathways downstream of the leptin-sensitive ARC neurons that participate in energy homeostasis are beginning to be dissected. Both AgRP/NPY neurons and POMC neurons originating in the ARC project heavily to the PVN and the perifornical hypothalamic area, regions long recognized to be important in the control of food intake. Neurons in the PVN synthesize many neuropeptides important in energy homeostasis, including corticotropin-releasing hormone, oxytocin, and thyrotrophin-releasing hormone. Each of these (and others) is a potential downstream target that could be regulated by input from ARC neurons, and each has been found to reduce food intake (for reviews, see Elmquist et al 1998, 1999; Trayhurn et al 1999; Woods et al 1998).

Peptides in the lateral hypothalamic area have also been implicated as downstream mediators of the actions of ARC neurons. Melanin-concentrating hormone (MCH) is expressed in the perifornical and lateral hypothalamic areas in neurons that receive synaptic input from both AgRP/NPY- and α-MSH–containing neurons (Elias et al 1998, Tritos et al 1998). MCH is an endogenous stimulant of feeding behavior (Qu et al 1996), and mice with a genetic MCH deficiency have reduced food intake and body fat stores, which suggests that MCH is another critical determinant of normal energy homeostasis (Qu et al 1996, Shimada et al 1998). Since hypothalamic MCH neurons project to diverse forebrain and hindbrain areas involved in food intake regulation, they may provide a key link between hypothalamic neurocircuits that respond to leptin and those that are involved in the short-term control of feeding. Other orexigenic [e.g. the orexins/hypocretins (de Lecea et al 1998, Sakurai et al 1998)] and anorexic [e.g. cocaine-amphetamine-related transcript (Kristensen et al 1998, Vrang et al 1999)] peptides
have also recently been discovered in the hypothalamus and have been linked to leptin’s actions (e.g. Lambert et al 1998, Trayhurn et al 1999).

Taken together, all these observations support a model in which the adipose tissue hormone leptin exerts opposing regulatory effects on ARC neurons containing NPY/AgRP on the one hand and melanocortins on the other. These neurons in turn project to secondary hypothalamic neuronal systems that are presumably regulated by inputs from myriad other systems pertinent to energy homeostasis. Ultimately, signals are generated that influence feeding behavior, energy expenditure, and the metabolic state of the individual. A major focus for the future is to identify critical neural networks in the brain that carry out these downstream effects. The importance of this objective is highlighted by the growing evidence that resistance to leptin, occurring at a “postreceptor” site in the CNS, is present in most forms of rodent obesity, and it likely exists in at least some forms of human obesity as well (Pi-Sunyer et al 1999, Trayhurn et al 1999, Woods et al 1998). We anticipate that the successful long-term treatment of obesity will require an appreciation of the multiple mechanisms responsible for this leptin resistance and the development of strategies to overcome it.

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